REMARKS

Claims 6, 37-40 and 57-67 were previously pending in this application. Claims 6, and 57-61 have been amended. Claim 6 has been amended to include the stringent hybridization conditions. Support for the amendment can be found at least at page 13, lines 17-20, of the specification as filed. Claim 6 has also been amended to remove part (c) to clarify the claim. Claims 57-61 have been amended to include the word "isolated" to clarify the identity of the nucleic acid molecule. Support can be found at least in the language of claim 6 as filed. As a result claims 6, 37-40, and 57-67 are pending for examination with claims 6 and 37 being independent claims. No new matter has been added.

Priority

The Examiner states that the specification lacks the requisite priority claim. Applicants respectfully point out that the correct priority claim was made by means of a preliminary amendment included on the utility patent applicant transmittal filed on February 11, 2000. The text of the inserted section was as follows:

Related Applications

This application is a divisional of U.S. Application Serial No. 08/948,705, filed on October 10, 1997, now pending.

Applicant amended the Related Applications section in the amendment mailed October 15, 2001 to read as follows:

Related Applications

This application is a divisional of U.S. Application Serial No. 08/948,705, filed on October 10, 1997, now issued as U.S. Patent 6,043,084.

The priority claim was acknowledged by the Examiner in the Office Action mailed March 27, 2002 in which the Examiner acknowledged the amendments made by Applicants in the previous response and also checked the box on the Office Action Summary indicating that "Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121".

Applicants submit that the correct priority claim is present in the specification and respectfully request the Examiner reconsider and withdraw the objection.

Claim Objections.

The Examiner objected to claim 6 because of punctuation informalities. Applicants submit that claim 6 as amended is correctly punctuated thereby obviating the grounds for the objection.

Rejections Under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claim 6 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Examiner indicated on page 4 of the Office Action that the meaning of section 6(c) is unclear with respect to the claimed genus of proteins. Applicants have amended claim 6 to remove sections (b) and (c), to clarify the scope and meaning of the claim.

The Examiner stated that "the claim as currently construed encompasses a genus of proteins with unrelated structures as long as they are cancer antigens that stimulate (an) immune response". (Office Action at page 4) The Examiner indicates that the proteins encoded by SEQ ID NO:1-4 do not share any structural similarities and concludes that the claim lacks adequate written description because it includes a series of structurally unrelated proteins (SEQ ID NOs:1-5). Applicants submit that based on Applicants' election of SEQ ID NO:2 as the species for examination, claim 6, which a generic claim, should be examined with respect to SEQ ID NO:2, not all of SEQ ID NO:1-5. Thus, the Examiner's comparison of structural relatedness of the proteins set forth as SEQ ID NO:1-5 is not relevant to the examination of the claim.

Applicants submit that the claimed invention is a genus of protein molecules that are encoded by SEQ ID NO:2 or by a nucleic acid molecule with a complementary sequence with sufficiently similar structure to permit hybridization to SEQ ID NO:2. SEQ ID NO:2 is disclosed in the specification as filed and is representative of the genus of nucleic acids that encode the claimed proteins. The nucleic acid molecules recited in the claims as encoding the claimed proteins are highly related in structure (nucleotide sequence) to SEQ ID NO:2.

The basic requirement of the written description requirement is that the claimed invention must be described clearly enough to allow one of ordinary skill in the art to recognize that the inventors invented the claimed invention. *Vas-Cath v. Mahurkar* 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991); *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gosteli* 872 F.2d 1008, 10 USPQ 2d 1614 (Fed. Cir. 1989). The requirement is based on the knowledge of the skilled artisan in the particular art: the applicant must convey to one of ordinary skill in the art through the disclosure in the invention that the applicant was in possession of the claimed invention. The *Lilly* case set forth written description requirements relating to nucleic acid sequences; this case does not prohibit definition of a genus of nucleic acid molecules by hybridization to a reference sequence. *Regents of the University of California v. Eli Lilly* 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997). The *Lilly* case merely states that a DNA molecule must be described by a precise definition, "such as by structure, formula, chemical name or physical properties." *Id.* A genus of nucleic acid molecules encoding a genus of proteins is not routinely defined in the art by a listing of sequences, chemical formulas or chemical names. Instead, the art routinely identifies nucleic acid molecules by hybridization to a particular nucleotide sequence. Hybridization conditions in combination with a reference sequence provide a precise definition of the claimed hybridizing nucleic acid molecules by physical properties.

The Examiner bases the rejection, in part, on the assertion that the function of the proteins, (e.g. biological and/or chemical) is not known (Office Action, page 4). Applicants respectfully submit that the relevant function of the claimed genus of cancer-associated proteins is the ability to stimulate a specific immune response, as evidenced by the methodology (SEREX) used to clone the nucleic acids encoding the proteins. This function is shared by each member of the genus. Applicants assert that the claims do not require any knowledge of any other functional activity of the proteins and that other biological function of the proteins is relevant to patentability of the claims.

The Examiner appears to suggests in the Office Action at page 5, that there are other proteins "without any structural similarities to instant proteins encoded by instant SEQ ID NOs:1-5 that are expressed in colon cancers and their cDNA could be screened by SEREX" as a basis for the rejection of the instant claims. Applicants are unclear as why the ability to use

SEREX to screen for other, unrelated cancer-associated proteins is relevant to the patentability of the claimed genus of proteins that are encoded by the disclosed SEQ ID NO:2 and structurally related nucleic acid molecules.

The Examiner also questions the inclusion of the degeneracy limitation in claim 6. Applicants submit that the general understanding of the degeneracy of the genetic code in the art is sufficient to allow one of ordinary skill to envision such sequence substitutions, but in an effort to expedite prosecution of the case, Applicants have amended claim 6 to remove the reference to degenerate molecules.

Applicants assert that claim 6 is drawn to a genus of proteins each of which is encoded by a nucleic acid that is highly structurally related to SEQ ID NO:2, and that the genus of proteins is adequately described through the recitation of a representative number of species as defined by reference sequence, SEQ ID NO:2 coupled with the use of stringent hybridization conditions that define the nucleic acid molecules by their physical properties. Applicants submit that the application recites sufficient distinguishing identifying characteristics for the claimed genus of protein molecules and that adequate written description of the claimed genus is provided.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection of claim 6 and 57-61 made under 35 U.S.C. §112, first paragraph, for lack of written description.

The Examiner rejected claims 6 and 57-61 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner indicates that this is a new matter rejection. Applicants have amended the claim to include the specific hybridization conditions set forth at column 22, lines 28-37 of US Patent No. 5,342,774. As the Examiner indicates in the Office Action at page 8, the instant specification at page 13, lines 17-21 incorporates the hybridization conditions of US Patent No. 5,342,774.

Applicants respectfully request that the Examiner withdraw the rejection of claims 6 and 57-61 under 35 U.S.C. §112, first paragraph, for lack of written description.

Enablement

The Examiner rejected claims 6, and 57-61 under 35 U.S.C. §112, first paragraph, as not enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner indicates at page 11 of the Office Action that claims 6 and 57-61 are interpreted as drawn to various proteins encoded by SEQ ID NO:1-5, and also encoded by nucleic acid molecules hybridizing to SEQ ID NO:1-5 under the recited conditions. Applicants note that, as described above, the election of SEQ ID NO:2 as the species for examination results in the pending claims under examination being drawn to the protein encoded by SEQ ID NO:2 and by nucleic acid molecules hybridizing under stringent conditions to SEQ ID NO:2.

Applicants submit that claims 57-61 should not be rejected as lacking enablement because each claim recites a specific sequence that encodes the protein. Therefore, claims 57-61 are enabled throughout their scope.

The Examiner accurately describes the factors to be considered to determine whether the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue, but fails to support the rejection with sufficient evidence to indicate that undue experimentation is required to practice the claimed invention. Applicants respectfully disagree with the Examiner's conclusions and maintain that full consideration of the *Wands* factors, in view of the state of the art at the time of filing, leads one to the reasonable conclusion that practicing the invention would not require undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The first factor considered by the Examiner is the nature of the invention. The Examiner indicates that the nature of the claimed invention includes "at least 5 proteins unrelated in terms of structure and/or their biological functions" (at Office Action, page 12). Applicants respectfully disagree with this interpretation. As described above, consonant with the species election, the claim for examination relate to a genus of protein molecules that are encoded by SEQ ID NO:2, or are encoded by a nucleic acid molecule with a complementary sequence with sufficiently similar structure to permit hybridization to SEQ ID NO:2. These are not proteins unrelated in structure, but rather are proteins closely related in structure as evidenced by the requisite high level of homology/identify of their encoding nucleic acid sequences. In addition, the claimed proteins are related in biological function in that each shares the biological function of being able to stimulate an immune response.

The next of the *Wands* factors to be considered by the Examiner are the state of the prior art and the relative skill of those in the art. These two *Wands* factors are crucial to any determination of undue experimentation. In the *Wands* case, for example, the court's decision turned on the "high level of skill in the art at the time the application was filed", and that "all of the methods needed to practice the invention were known." *Wands* at 740, 8 USPQ2d at 1406. Applicants maintain that the same conclusions with respect to the state of the art and the level of skill in the art are true in the instant case, and therefore must weigh heavily in favor of a finding that undue experimentation is not required.

The level of skill in the art has an important effect on the amount of guidance which must be provided to enable the invention. As the court stated in *In re Howarth*, "[i]n exchange for the patent, [the applicant] must enable others to practice his invention. An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*, 654 F.2d 103, 105 (C.C.P.A. 1981). For the standard procedures required to practice the claimed invention, the level of skill in the art is high. Applicants maintain that the person of skill in the art would know how to make and use the claimed proteins of the invention, having in hand Applicants' disclosure. The Examiner suggests that this determination would require experiments involving clinical samples. Applicants suggest that clinical samples may not be required, but rather one of ordinary skill in the art would use routine hybridization of DNA, clone selection, and protein expression methodology to make and use the proteins of the invention. Applicants assert that even if the determination did require experiments involving clinical samples – such procedures would have been routine for those skilled in the art at the time of filing.

With regard to the level of predictability in the art, the Examiner suggests that the level of predictability is low. Applicants respectfully contend that given the disclosure of SEQ ID NO:2 as the reference sequence for nucleic acids that encode the claimed proteins, there is more predictability at to the acquisition of encoded proteins that stimulate an immune response than is suggested by the Examiner. Applicants submit that making a protein from a DNA sequence is predictable. The Examiner also contends that the scope of the claims is broad and includes unknown species. Applicants maintain that the claims are not excessively broad because they encompass a genus of protein molecules that is well defined by the claim limitations provided.

With respect to the working examples *Wands* factor, the court in *In re Wright* stated that "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright* 999 F.2d 1557, 1561, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993) *citing In re Marzocchi* 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971). Applicants have provided broad terminology which is readily understandable to one of ordinary skill in the art. In addition, the specification provides the sequence of SEQ ID NO:2 and teaches how one of ordinary skill would use the sequence via routine procedures to make the claimed invention.

In summary, a full analysis of the *Wands* factors strongly favors a conclusion that only routine experimentation would be required of one of ordinary skill in the art to practice the claimed invention throughout its scope.

Accordingly, in view of the analysis above, Applicants respectfully request that the Examiner withdraw the rejections of claims 6 and 57-67 made under 35 U.S.C. §112, first paragraph.

The Examiner rejected claims 37-40 and 62-61 under 35 U.S.C. §112, first paragraph, as not enabled by the specification. Applicants respectfully traverse the rejection.

The claims under examination (in view of the species election) are drawn to a composition comprising a plurality of immunogenic peptides derived from the amino acid sequence of a protein encoded by SEQ ID NO:2.

The Examiner states that "it is not clear if CTLs could be generated using any fragment of SEQ ID NO:1-5". (Office Action, page 15) Applicants respectfully disagree with this conclusion. First, as noted above, Applicants have demonstrated that the protein encoded by SEQ ID NO:2 is expressed, because without protein expression, no antibodies would have been generated in cancer patients. Second, this same concept provides evidence that the peptides bound to and were presented by one or more MHC molecules presented on the surface of cells, in order to provide T cell help for the B cell antibody response.

Third, the law of enablement does not require a description of every aspect of the claimed invention, because it is expected that one of ordinary skill in the art can exercise routine experimentation to make and use the claimed invention. In this regard, Applicants note that it is

routine in the art of cancer immunity to derive peptides from the amino acid sequence of a protein known or suspected to be immunogenic. In this case, Applicants have provided evidence of the immunogenicity of the claimed protein by virtue of the protein's isolation using the SEREX method. Chen et al (*Proc. Nat'l. Acad. Sci. USA* 94:1914-1918, 1997) described the implications of antibody recognition of cancer-associated proteins: "a humoral response implies T cell recognition of the detected antigens by helper T cells. Thus, even though the antigens are initially identified by antibodies, the method reveals tumor products that can then be analyzed in the context of cell-mediated immunity." (page 1914, right column) The analysis for identifying MHC binding peptides from a protein sequence is well known in the art. For example, see Rammensee H, et al., *Immunogenetics*. 1999 Nov;50(3-4):213-9 and Parker KC, et al., *J Immunol*. 1994 Jan 1;152(1):163-75, copies of which are provided herewith for the Examiner's convenience. Accordingly, it would require only routine experimentation for one of ordinary skill in the art to identify peptides useful in the claimed compositions.

Therefore, Applicants respectfully request that the Examiner reconsider and withdrawn the rejections made under 35 U.S.C. 112, first paragraph for lack of enablement.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 57-61 under 35 U.S.C. §112, second paragraph, as indefinite.

The Examiner indicated that it was unclear which nucleic acid molecule of claim 6 case referred to in the recited limitation of claims 57-61. Applicants have amended claims 57-61 to include the word "isolated" to clarify the identity of the nucleic acid molecule.

On the basis of the amendment, Applicants respectfully request that the Examiner withdraw the rejection of claims 57-61 under 35 U.S.C. §112, second paragraph as indefinite.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Matthew J. Scanlan et al., Applicant

By: _____

MaryDilys S. Anderson, Reg. No.52,560
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone: (617) 720-3500

Docket No. L0461.70081US00
Date: August 25, 2004
x08/25/04x